UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte SUZANNE DE LA MONTE and JACK R. WANDS

Appeal No. 2004-2135[1]
Application No. 09/964,678

HEARD: April 19, 2005

Before WILLIAM F. SMITH, SCHEINER and GRIMES, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of claims 7-9, 14-16 and 35-40, all the claims remaining in the application.

AD7c-NTP cDNA, isolated from an Alzheimer's disease [AD] brain expression library, encodes a protein which is "expressed in neurons, and over-expressed in brains with AD." Specification, page 17. According to appellants, "*In situ* hybridization and immunostaining studies localized AD7c-NTP gene expression in neurons, and confirmed the over-expression associated with AD neurodegeneration . . . suggest[ing] that abnormal AD7c-NTP gene expression is associated with AD neurodegeneration . . . [and that] abnormal expression of AD7c-NTP is a phenotype associated with Alzheimer's

[1] This appeal is related to an appeal in Application Serial No. 09/380,203 (Appeal No. 2005-0807). We have considered the two appeals together.

disease." Id., page 18. AD7c-NTP has been observed to "induce neu[r]itic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles, and/or irregular swollen neurites in a host which expresses the [protein]." Id., pages 18-19.

The present invention is directed to a non-human transgenic animal whose germ and somatic cells comprise AD7c-NTP DNA (i.e., SEQ ID NO:1) or a DNA molecule which is at least 90% homologous to SEQ ID NO:1, wherein the DNA molecule is over-expressed in one or more cells of the animal, and codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells. In addition, the invention is directed to a method of using the transgenic animal to screen candidate drugs "potentially useful for the treatment or prevention of" Alzheimer's disease.

Claims 7, 8, 14, 15, 36 and 37 are representative of the subject matter on appeal:

7. A transgenic non-human animal, all of whose germ and somatic cells comprise the DNA molecule of SEQ ID NO:1 or a DNA molecule which is at least 90% homologous thereto, wherein said DNA molecule is over-expressed in one or more cells of said transgenic animal, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

8. The transgenic non-human animal of claim 7, wherein the DNA molecule contained in each germ and somatic cell has SEQ ID NO: 1.

14. An *in vivo* method for screening a candidate drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, and glioblastomas, said method comprising:

(a) administering a candidate drug to the transgenic animal of claim 7, and

(b) detecting at least one of the following:

(i) the suppression or prevention of expression of the protein coded for by the DNA molecule contained by said animal; or

(ii) the increased degradation of the protein coded for by the DNA construct contained by said animal;

due to the drug candidate compared to a control animal which has not received the candidate drug.

15. The method of claim 14, wherein the DNA construct contained by said animal has SEQ ID NO: 1.

36. The transgenic non-human animal of claim 7, wherein said activity of AD7c-NTP possessed by said DNA molecule when over-expressed in neuronal cells is selected from the group consisting of neuritic sprouting, nerve cell death, nerve cell degeneration, neurofibrillary tangles and irregular swollen neurites.

37. An *in vivo* method for screening a candidate drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, and glioblastomas, said method comprising:

(a) adminstering a candidate drug to the transgenic animal of claim 7, wherein said transgenic animal exhibits at least one of neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons; and

(b) detecting the reduction of frequency of at least one of neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in the host due to the drug candidate compared to a control animal which has not received the candidate drug.

DISCUSSION

Claims 7, 9, 14, 16, 35 and 36 stand rejected under the first paragraph of 35 U.S.C. § 112, as lacking adequate written description. Claims 7-9, 14-16 and 35-40 stand rejected under the first paragraph of 35 U.S.C. § 112, as lacking enablement.

We reverse these rejections.

Written Description

According to the examiner, "[t]he specification provides sufficient description of SEQ ID NO: 1 . . . [which] codes for an AD7c-NTP protein" (Answer, page 4), but not for "a genus of DNA molecules with 90% homology to SEQ ID NO:1 that codes for a protein that has an activity of AD7c-NTP when over expressed in neuronal cells" (id., page 5). The examiner asserts that "[t]he skilled artisan cannot envision the detailed structure of a genus of a DNA molecule, which displays at least 90% homology to SEQ ID NO:1 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification." Id., page 6.

"The 'written description' requirement serves a teaching function, . . . in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" University of Rochester v. G.D. Searle & Co., Inc., 358 F.3d 916, 922, 69 USPQ2d 1886, 1891 (Fed. Cir. 2004) (citation omitted). Another "purpose of the 'written description' requirement is . . . [to] convey with reasonable clarity to those skilled in the art that, as of the filing date [ ], [the applicant] was in possession of the invention." Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). See also Enzo Biochem Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1329, 63 USPQ2d 1609, 1617 (Fed. Cir. 2002). The requirement is satisfied when the specification "set[s] forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed." University of Rochester, 358 F.3d at 928, 69 USPQ2d at 1896. Whether or not a specification satisfies the requirement is a question of fact, which must be resolved on a case-by-case basis (Vas-Cath, 935 F.2d at 1562-63, 19 USPQ2d at 1116), and it is the examiner's "initial burden [to] present[ ] evidence or reasons why persons skilled in the art would not recognize in the disclosure a description of the invention defined by the claims" (In re Wertheim, 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)).

"[A]pplicants have some flexibility in the 'mode selected for compliance' with the written description requirement" (University of Rochester, 358 F.3d at 928, 69 USPQ2d at 1896); it is well settled that actual reduction to practice is not necessary to satisfy the requirement (id., at 926, 69 USPQ2d at 1894). In University of California v. Eli Lilly and Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), the court discussed the application of the written description requirement to inventions in the field of

biotechnology, stating that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405. The court also stated that

> a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material" (id.), but "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

Subsequently, the court clarified that "[not] all functional descriptions of genetic material fail to meet the written description requirement," for example, "the written description requirement would be met for [a claim] . . . if the functional characteristic . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." Enzo Biochem, 296 F.3d at 1324-25, 63 USPQ2d at 1613.

Here, all of the polynucleotides in the claimed genus have a certain amount of structural commonality (all are "at least 90% homologous" to SEQ ID NO:1 (the cDNA encoding AD7c-NTP)), and all encode proteins which have at least one defined functional characteristic, "an activity of AD7c-NTP when over-expressed in neuronal cells." The specification describes methods of isolating DNA molecules at least 90% homologous to SEQ ID NO:1; specific activities of AD7c-NTP; and assays to confirm those activities. Specification, pages 18-20, e.g. Again, as explained in Lilly, a genus of polynucleotides can be described by a representative number of polynucleotides, defined by sequence, or sharing common structural features which constitute a substantial portion of the genus; and, as explained in Enzo, a genus may be described by means of a functional characteristic coupled with a disclosed correlation between that function and a known or disclosed structure.

Whether the level of disclosure in the specification would have allowed one skilled in the art to recognize that the inventor invented what is claimed is a question of fact. The USPTO has summarized a number of factors to be considered in making this determination; they include "the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." Guidelines for Examination of Patent applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (Jan. 5, 2001). "Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." Id.

Rather than providing an analysis of these or any other factors, the examiner simply asserts that "an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the claimed invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of DNA sequences that must exhibit the disclosed biological functions as contemplated by the specification." Answer, page 5.

This conclusory statement is insufficient to meet the examiner's initial burden of establishing that one skilled in the art would not have recognized that appellants were in possession of what is claimed. Accordingly, the rejection is reversed.

Enablement

Claims 7-9, 14-16 and 35-40 stand rejected under the first paragraph of 35 U.S.C. § 112, "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art . . . to make and/or use the invention." Answer, page 6. The examiner has two principal concerns: that it would require undue experimentation to "arrive at other DNA molecules with at least 90% homology to SEQ ID NO:1 [ ] having SEQ ID NO:1 activity when over-expressed in neuronal cells" (Answer, page 8); and that it would require undue experimentation to produce transgenic animals comprising "SEQ ID NO:1 or a sequence with 90% homology thereto, which over-expresses the transgenic sequence such that a phenotype occurs" (id., page 10).

"The first paragraph of 35 U.S.C. § 112 requires, inter alia, that the specification of a patent enable any person skilled in the art to which it pertains to make and use the claimed invention. Although the statute does not say so, enablement requires that the specification teach those in the art to make and use the invention without 'undue

experimentation.' In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).[2] That some experimentation may be required is not fatal; the issue is whether the amount of experimentation is 'undue.'" In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991) (emphasis in original). Nevertheless, "[w]hen rejecting a claim under the enablement requirement of section 112," it is well settled that "the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement." In re Wright, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Thus, the issue here is not whether appellants have established that the disclosure is enabling for the claims, rather, the issue is whether the PTO has met its "initial burden of setting forth a reasonable explanation as to why" it is not. With this in mind, we consider the reasons given in support of the examiner's conclusion that it would have required undue experimentation to practice the claimed invention.

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> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims (footnote omitted).
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> In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

With respect to the examiner's first concern – transgenic animals comprising transgenes at least 90% homologous to SEQ ID NO:1 – the examiner argues that "[t]he specification does not disclose which nucleotides . . . [are] essential . . . to make a representative number of DNA molecules with 90% homology to SEQ ID NO:1" (Answer, page 7) and the activity of AD7c-NTP, because "the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) [is] not well understood and [is] not predictable" (id.).

In response, appellants point out that "numerous methods [ ] were available in the art at the time of the application that could have been used to produce DNA molecules 90% homologous to SEQ ID NO:1" and "methods for determining whether a given DNA molecule codes for a protein that has an activity of AD7c-NTP are set forth in the specification" (Brief, page 31). Appellants argue that "[a] skilled artisan [could] easily screen for DNA molecules . . . at least 90% homologous to SEQ ID NO:1 and that encode proteins having AD7c-NTP activity when over-expressed in neuronal cells" and that "[s]uch screening, even if it resulted in the identification of [a] molecule not having the desired activity, is routine" (id., page 33). We agree with appellants that "any uncertainty . . . associated with predicting protein function from sequence data is irrelevant" (id.) in the context of the claimed invention. In view of the art-known methods of making DNA molecules at least 90% homologous to SEQ ID NO:1 and the disclosed screening methods, the examiner has not adequately shown that more than routine experimentation would have been required to practice the claimed invention.

With respect to the second issue – producing transgenic animals per se – the examiner notes that there are no working examples of transgenic animals in the specification (Answer, page 26), and argues essentially that "producing transgenic

animals with a predictable phenotype was considered unpredictable as exemplified by" "the art of record at the time the application was filed" (id., page 9).

Before we address the art of record, however, it is necessary to address the examiner's treatment of the claims. The examiner acknowledges that "the claimed transgenic animal is not limited to expression of [AD7c-NTP] at a level resulting in a specific phenotype" (Answer, page 10), but nevertheless treats each of the claims as requiring "a phenotype observed with Alzheimer's disease, neuroectodermal tumor, malignant astrocytoma[ ], [or] glioblastoma[ ]" (id., pages 9 and 23), because "it is unknown what other purpose the transgenic animal would serve if the transgene . . . is not expressed at a sufficient level for a resulting phenotype" (id., page 11).

However, the specification teaches that the transgenic animals may be used to determine whether a candidate drug causes decreased expression or increased degradation of the protein encoded by the transgene (see e.g., page 21 of the specification). This is consistent with appellants' assertion that "the only characteristic that the transgenic animals encompassed by . . . claims 7-9, 14-16, 35, 36, 39 and 40 need [ ] in order to be useful for the contemplated screening methods is that they express the DNA of SEQ ID NO:1 or a DNA molecule that is at least 90% homologous thereto" that codes for a protein that has an activity of AD7c-NTP (id., page 14). We agree with appellants that these claims "do not require that the transgenic animals exhibit a specific phenotype" (Brief, page 13), and that the examiner's argument is without merit with respect to claims 7-9, 14-16, 35, 36, 39 and 40.

Claims 37 and 38, on the other hand, require a transgenic animal exhibiting "at least one of neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, [and] irregular swollen neurites and axons[.]" The examiner cites several

references as evidence of the unpredictability of producing a transgenic animal with a desired phenotype: Polejaeva[3] as evidence that pro-nuclear injection of zygotes to produce transgenic animals "suffers from several serious limitations[,]" for example, random integration of the transgene and possible disruption of essential endogenous DNA sequences or activation of cellular oncogenes (Answer, page 9); Trojanowski[4] as evidence that "in vitro paradigms have limited utility as models of in vivo mechanisms of neurodegeneration" (id., page 10); Wall[5] and Houdebine[6] as evidence that transgenic constructs must be designed case by case to obtain good expression of the transgene (id., page 12); and Mullins[7] as evidence that transgene expression varies according to the particular host species (id.).

Appellants argue that the references cited by the examiner "describe several instances in which transgenic animals exhibiting a desired phenotype were successfully produced" (Brief, page 45), and that these references, "rather than demonstrating that the production of transgenic animals with a particular phenotype requires undue experimentation, merely indicate that certain technical issues should be considered in order to successfully produce transgenic animals exhibiting a certain phenotype" (id.). Moreover, appellants' specification refers to several methods of making transgenic

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[3] Polejaeva et al., "New Advances in Somatic Cell Nuclear Transfer: Application in Transgenesis," Theriogenology, Vol. 53, pp. 117-126 (2000).

[4] Trojanowski et al., "Transgenic Models of Tauopathies and Synucleinopathies," Brain Pathology, Vol. 9, pp. 733-739 (1999).

[5] Wall, "Transgenic Livestock: Progress and Prospects for the Future," Theriogenology, Vol. 45, pp. 57-68 (1996).

[6] Houdebine, "Production of Pharmaceutical Proteins from Transgenic Animals," Journal of Biotechnology, Vol. 34, pp. 269-287 (1994).

[7] Mullins et al., " Transgenesis in the Rat and Larger Mammals," Journal of Clinical Investigation, Vol. 97, No. 7, pp. 1557-1560 (April 1996).

animals and cites many examples in the scientific literature of the successful production of transgenic animals with specific phenotypes, using those methods (see, e.g., page 20 of the specification). Additional examples of successful production of transgenic animals exhibiting a phenotype conferred by a transgene (including animals exhibiting neurological phenotypes associated with Alzheimer's disease) were provided by appellants during prosecution of this application, and were relied on in appellants' arguments here (see pages 28-29 of the Brief).

The examiner "acknowledge[s] that there are other types of transgenic animals cited in the art[,]" but argues that they were produced using "distinct materials (different gene, different disease, etc.)" (Answer, pages 28) and "there is no[ ] universal protocol" for making transgenic animals (id., page 29); thus, "one skilled in the art can not reasonably extrapolate from one type of transgenic animal to another" (id.). Nevertheless, even if we accept for the sake of argument that the evidence of record shows that this art requires a certain amount of experimentation, and that many attempts are initially unsuccessful, the examiner has not explained why the amount or type of experimentation required would be considered undue. As explained in PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), undue experimentation has little to do with the quantity of experimentation; it is much more a function of the amount of guidance or direction provided:

> [T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984). The Patent and Trademark Office Board of Appeals summarized the point well when it stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982).

We agree with appellants that the examiner has not established that producing a transgenic animal with a particular phenotype would have required "a degree of experimentation that would be regarded as undue in the art" at the time of the invention. Brief, page 45.

In our view, the reasons cited in support of the examiner's rejection are insufficient to support the examiner's conclusion that the claims are not enabled by the specification. Accordingly, the rejection of claims 7-9, 14-16 and 35-40 under the first paragraph of 35 U.S.C. § 112 is reversed.

AN ADDITIONAL ISSUE

We note the examiner's observation that "[t]he USPTO written description guidelines for example 14[8] do not correlate to the written description in [ ] appellants' specification" because "90% homology is different than 95% homology" (Answer, page 16). We further note that this observation was not included in the examiner's rejection, but was made in response to appellants' argument that the written descriptive support for the present claims is similar to that found to be adequate in the synopsis. Nevertheless, this observation, coupled with the lack of any factual analysis in the statement of the rejection, leaves the unfortunate impression that a per se rule is being

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[8] Example 14 of the USPTO's Synopsis of Application of Written Description Guidelines, available at http://www.uspto.gov/web/menu/written.pdf

applied to the claims – i.e., claims that do not narrowly track one of the examples in the synopsis lack adequate written descriptive support. As discussed above, compliance with the written description requirement is a question of fact, which must be resolved on a case-by-case basis; application of a per se rule would be improper.

CONCLUSION

The rejections of the claims under the first paragraph of 35 U.S.C. § 112 as lacking written descriptive support and lacking enablement are reversed.

REVERSED

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Eric Grimes
Administrative Patent Judge

BOARD OF PATENT APPEALS AND INTERFERENCES

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